REMARKS

Claims 1-10, 15-26, 28, 31-45, 47, 50-59, 61 and 64-70 are pending. Claims 1-7, 10, 15-22, 31-42, 45, 50-55, 64-66 and 68 are withdrawn from consideration as being drawn to non-elected inventions. Claims 8, 9, 23-26, 28, 43, 44, 47, 56-59, 61, 67, 69 and 70 are rejected.

Objections to the Claims

Claim 26 is objected to for a minor informality in claim language. Applicants herein change the claim language to recite "the method" as suggested by the Examiner thereby obviating the rejection.

Rejection under 35 U.S.C. 112, 1st Paragraph

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, and 67-70 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement for the treatment of Alzheimer's disease or other degenerative cognitive diseases, such as AAMI, MCI, CVD.

The Examiner alleges that the specification does not enable any person skilled in the art to practice the invention in scope with the claims. More particularly, the Examiner alleges that since ***"treatment"*** encompasses "the identification of treatment populations at risk for a neurodegenerative condition prior to development of a neurodegenerative condition, e.g. prior to development of MCI, AD or CVD", it would take undue experimentation by the skilled artisan to determine how the presently claimed active agent(s) could be used to treat conditions as elusive and difficult to diagnose as those recited in the claims. The Examiner has outlined various reasons as to why the breadth of the claims are not allowable. In particular the Examiner alleges that:

> *"The term 'treat' in the present claims is a term that, interpreted in its broadest sense in accordance with the MPEP at §2111, circumscribes various scenarios, including the amelioration of symptoms, the disappearance of symptoms, slowing or halting the progression of such a disease or identifying patients at risk for a neurodegenerative condition prior to developing such a neurodegenerative condition and treating them with the presently claimed combination of active agents. Identifying patients at risk*

prior to developing the disorder would essentially amount to the prevention of such a disorder in those patients. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, the development, progression or worsening of Alzheimer's disease would be prevented, slowed or arrested, that the symptoms associated with such a condition would disappear or be significantly lessened and that there would be a reasonable guarantee that Alzheimer's disease would not progress to the point of being incapable of basic human function. Such a situation is sufficiently unusual that data would need to be shown in order to establish that Alzheimer's disease could be kept from ever developing, progressing or worsening or that the symptoms directly associated with such a condition would be eradicated or significantly lessened through the administration of the claimed active agent. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as Alzheimer's disease, the specification, which lacks an objective showing that such a disease could be treated in such a manner, is viewed as lacking an enabling disclosure of the same.

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...A diagnosis of Alzheimer's disease is tentative, at best, until confirmation of the diagnosis can be confirmed by the presence of amyloid deposits in the brain at autopsy (see Cecil's Textbook of Medicine, 'Differential Diagnosis', page 2043 at column 1)."

Applicant intends that "treatment" include amelioration of symptoms and/or slowing of progression of the condition. For instance, "treatment" (amelioration) of symptoms includes a reduction of cognitive disability, a reduction of functional disability, and a reduction of behavioral disturbances. All of these symptomatic areas may be measured by the NYU-CIBIC Plus assessment. *See, e.g.* Reisberg *et al.*, *Alzheimer Disease and Associated Disorders*, 1997, 11 :(Suppl. 3), 8-18; Reisberg *et al.*, Clinician's Interview–Based Impression of Change-Plus. In: Guide to Assessment Scales in Dementia. C. Kelly, G. Newton-Howes (Eds.) London, U.K: Science Press Ltd., 2004, 9-10, and 21 page scale reproduction. These symptoms are also measured with other assessment scales commonly used in Alzheimer's disease, MCI and AAMI. For purposes of the instant invention, Applicants also intend "treatment" to include a slowing of the progression of these conditions. This slowing can be measured by the same instruments as those used in assessing symptomatic amelioration. *See, e.g.* Reisberg *et al.*, *Archives of Neurology,* 2006, 63: 49-54. The term "treatment" is clearly

defined in paragraph [0022] of the specification.

The Examiner alleges that the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's disease and that post mortem analysis of brain tissue for the characteristics of amyloid plaques is considered necessary (*citing*, Gauthier, *et al.*, *Can. Med. Assoc. J,* Oct. 15, 1997, 157(8): 1047-52; Greicius, *et al.*, *J Neurol. Neurosurg. Psychiatry*, 2002 Jun; 72(6): 691-700 and Gasparini, *et al.*, *FASEB J.,* 12, Jan. 1998, pp. 17-34). Applicant submits that at the present time, there is a consensus that Alzheimer's disease is a clinico-pathologic syndrome which can be diagnosed on the basis of its characteristic clinical features during the patient's lifetime. Applicant has been involved in one consensus which emphasizes this current truth and practice. *See*, Reisberg, *et al.* "Diagnosis of Alzheimer's disease: Report of an International Psychogeriatric Association Special Meeting Work Group Under the Cosponsorship of Alzheimer's Disease International, the European Federation of Neurological Societies, the World Health Organization, and the World Psychiatric Association." *International Psychogeriatrics,* 1997, 9(Suppl. 1): 11-38. This consensus from many of the major worldwide organizations states

> *There is agreement that Alzheimer's Disease is a characteristic clinicopathologic entity that is amenable to diagnosis. The diagnosis of Alzheimer's Disease should no longer be considered one of exclusion. Rather, the diagnostic process is one of recognition if the characteristic features of Alzheimer's Disease and of conditions that can have impact on presentation or mimic aspects of the clinicopathologic picture.*

Small *et al.,* reached a similar conclusion in their 1997 consensus published in JAMA and cited by the examiner. *See*, Small *et al. JAMA* 1997; 278:1363-1371.

Applicant further submits that Mild Cognitive Impairment is also a commonly diagnosed condition at the present time. A complete discussion of various approaches to MCI diagnosis can be found in, for instance, Gauthier, *et al.*, on behalf of the participants of the IPA Expert Conference on MCI. Lancet, 2006, 367: 1262-1270. The many publications on Mild Cognitive Impairment are testimony to the recognition by numerous journals of our ability to diagnose this condition. *See, e.g.* Franssen, *et al.*, *Journal of the American Geriatrics Society,* 1999, 47: 463-499; Kluger, *et al.*, *Journal of Gerontology: Psychological Sciences*, 1997, 52B:P28 - P39.

In addition, there has been a longstanding recognition of the ability to diagnose Age Associated Memory Impairment. *See, e.g.,* Reisberg, *et al., Developmental Neuropsychology,* 1986, 2:401-412; Reisberg, *et al., Drug Development Research,* 1988, 15:101-114. Therefore, there is a consensus that the conditions that are described in the present application can be readily recognized and diagnosed by clinicians.

The Examiner further alleges that Applicant has merely disclosed that one may treat a patient with the agents claimed, but that such disclosure is not adequate direction or guidance as to how the proposed combination of agents could be employed to accomplish the treatment of these patients in a predictable manner. The Examiner alleges that there is no reasonable guarantee that the progression of the noted conditions may be prevented, slowed or arrested. Furthermore, there is allegedly no protocol for carrying out such studies. The Examiner alleges that in light of the state of the art, which recognizes the unpredictable nature of these disorders or conditions, the Office would require appropriate data to support the use of the agents as claimed.

Applicant submits that the present invention is based in part upon the discovery of a new mechanism of disease based upon the process of "Retrogenesis." As stated in the application, "retrogenesis" may be defined as the process by which degenerative mechanisms reverse the order of acquisition in the normal human development. This process was discovered only after lengthy research findings. The present invention is therefore based in

part upon the discovery of a biomolecular basis for this previously unknown disease process. For instance, in 1985 it was first noted that the functional stages of Alzheimer's disease reversed the order of acquisition of the same functions in normal human development. See, Reisberg *et al.*, "Functional degenerative stages in dementia of the Alzheimer's type appear to reverse normal human development." In: *Biological Psychiatry*, 1985, Vol. 7, C. Shagass, *et al.*, (Eds.). New York: Elsevier Science Publishing Co., 1986, pp. 1319-1321. Then, it was recognized that the time course of loss of function in Alzheimer's disease closely mirrored the time course of acquisition of same functions in normal human development. *See*, Reisberg *et al.*, "Dementia: A systematic approach to identifying reversible causes." *Geriatrics*, 1986, 41 (4): 30-46. Later, Applicant took psychological testing measures which had been previously applied to infants and small children and adapted them for use in what was then called "untestable" Alzheimer's disease. These adaptations were successful. *See*, Sclan, *et al.*, *Psychiatric Journal of the University of Ottawa,* 1990, 15:221-226; Auer *et al.*, *Journal of the American Geriatrics Society,* 1994, 42:1266-1272. Applicant found that the infant test measures showed just as robust relationships to the functional course of Alzheimer's disease as standard testing for Alzheimer's disease did earlier in the course of the disease when the standard testing had not bottomed out. This novel discovery resulted in a patent regarding the utility of developmental neuropsychological measures for AD and dementia assessment. *See,* Sclan, *et al.*, U.S. Patent No. 5,082, 446.

Subsequently, it was found that a childhood intelligence test, the Binet intelligence test, was also an excellent marker of the course of moderate to severe AD, at least as good as standard AD tests. *See, e.g.* Shimada *et al.*, *Psychogeriatrics, 2*003, 3:82-87. Applicant also found that infantile neurological reflexes emerge in Alzheimer's disease patients at the point in the illness corresponding to the functionally based developmental age of the patient. *See, e.g.* Franssen *et al.*, *Archives of Neurology,* 1991, 48:148-154; Franssen *et al., Archives of Neurology,* 1993, 50:1029-1039; Franssen *et al.*, *Journal of Geriatric Psychiatry and Neurology*, 1997, 10:22-28. These discoveries resulted in Franssen *et al.*, U.S. Patent No. 5, 150, 716. Further, subsequent inventions involving the utility of infantile, developmental reflexes in diagnosing the origins of incontinence in dementia patients were the subject of Franssen *et al.*, U.S. Patent No. 5,826,585. Also, it was found that the developmental age of the AD

patient was useful in interpreting behavioral disturbances in these patients. *See, e.g.* Reisberg *et al.*, *International Academy for Biomedical and Drug Research,* 1998, 13:102-109. In addition, it was found that a science of AD management based upon these discoveries of the retrogenic AD process could be developed. *See, e.g.* Reisberg *et al.*, President's Report: Towards a science of Alzheimer's disease management: A model based upon current knowledge of retrogenesis. *International Psychogeriatrics,* 1999, 11: 7-23; Reisberg *et al.*, *American Journal of Alzheimer's Disease,* 2002, 17:202-212. Copending U.S. Utility Patent Application Serial No. 10/632,558 filed July 31, 2003 is directed to an invention based upon these discoveries.

The present invention is based in part upon the discovery of the biomolecular basis for this process of retrogenesis. Specifically, Applicant discovered that *"the most metabolically active regions of the brain in AD, which are most capable of responding to a mitogenic stimulus are the most vulnerable in AD."* Further information regarding this discovery is presented in Reisberg *et al.*, *American Journal of Alzheimer's Disease, 2002*, 17:202-212. The present invention is further based in part upon Applicant's discovery of a decrease in metabolic activity as the stages of AD progressed. *See, e.g.* Reisberg *et al.*, Am J Psychiatry, 1982, 139:1136-1139. Applicant further discovered that metabolic activity in the brains of normal aged patients can predict decline in cognition to MCI or dementia, generally AD, 4 years later. Therefore, metabolic changes appear to be precursors of the process of cognitive decline in both MCI and dementia. *See, e.g.* de Leon, *et al.*, *Proceedings of the National Academy of Sciences,* 2001, 98:10966-10971.

Applicant's discovery that the most metabolically active regions of the brain are the first to be affected by AD pathology, has recently been confirmed by the work of Buckner, *et al.* (*Journal of Neuroscience*, 2005) who found that the regions of the brain which are the most metabolically active during the resting (so call default) state in normal young adults, are the regions where the amyloid plaques of AD develop decades later.

Applicant is also involved in studying the nature of the basic pathologic process and pathologic changes in AD and the relationship of these changes to the functionally based retrogenic stages, known as the Functional Assessment Stages (FAST stages) of AD. Applicant discovered, using postmortem studies of hippocampal brain tissue of AD patients, that the volume changes in hippocampal brain regions relate very strongly to the retrogenic FAST stages. *See, e.g.* Bobinski *et al.*, *Dementia,* 1995, 6:205-210. Applicant further discovered that the neurofibrillary changes in AD and, more specifically, the percentage of remaining cells in the hippocampal brain regions with neurofibrillary changes, relate strongly to the retrogenic FAST stage of AD. *See, e.g.,* Bobinski *et al.*, *Journal of Neuropathology and Experimental Neurology*, 1997, 56:414-420.

In accord with Applicant's studies discussed above, Applicant has discovered that there is a strong relationship between the retrogenic process in AD and neuronal losses, hippocampal function volume losses and neurofibrillary changes (neurofibrillary tangles, NFT) in the disease. *See, e.g.,* Bobinski *et al.*, *Journal of Neuropathology and Experimental Neurology*, 1997, 56:414-420. In summary, numerous findings and discoveries outlined herein over the past two to three decades have lead to the discoveries described in the present application. A brief review of the salient findings includes:

1. The discovery and validation of the retrogenic process in AD.
2. The discovery that metabolic deficits occur in the brain with the evolution of MCI and AD.
3. The discovery of abnormalities in the cell cycle in aging and AD.
4. The discovery that metabolic deficits precede behavioral manifestations of AD.
5. The discovery that the retrogenic process and the cell cycle abnormalities can explain the pathologic nature of AD, including the cell losses in specific brain regions, and the neurofibrillary tangles.
6. The discovery that the metabolic patterns in the brain of normal subjects and subsequent changes in AD, relate to the β-amyloid plaques in AD.

It should also be noted that the reactivation of cell cycle caused by stressors results not only in tau hyperphosphorylation and neuronal tangles, but also in cell death by other apoptotic like mechanisms.

The present invention therefore provides methods for treating AD with cell cycle inhibitors. However, cell cycle inhibitors alone may be insufficient. Effective treatment may also require mitigation of the stressors stimulating the cell cycle response in the neurons. Otherwise, the reactivation of the cell cycle may drive a neuron to an apoptotic (death) response, even with the administration of a cell cycle inhibitor. Specifically, mitigation of the inflammatory process resulting from presynaptic neuronal injury and the excitotoxicity resulting from presynaptic neuronal injury may be necessary. The present invention is based in part upon this discovery. Specifically, Applicant has confirmed the utility of the excitotoxicity antagonist, memantine in the treatment of AD. *See, e.g.,* Reisberg *et al., New England Journal of Medicine*, 2003, 348:1333-1341; Reisberg *et al., Archives of Neurology,* 2006, 63: 49-54. As the present invention teaches, the treatment of AAMI, MCI, AD, CVD and other retrogenic dementias should be accompanied by agents that mitigate stressors which stimulate the cell cycle response, such as the NMDA receptor, glutamate excitotoxicity antagonist, memantine.

Rejection Under 35 U.S.C.112, 2nd Paragraph

Claims 8-9, 43-44, 47 and 67-68 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. The Examiner notes the term ***"related retrogenic diseases"*** alleging that these "related" diseases are not adequately defined such that they fall within the scope of the invention. The Examiner notes that Applicant's reliance upon paragraph [0033] of the present specification to define the term "retrogenesis" and to further state that the retrogenic process "is also related to recent findings regarding the molecular biology of normal cellular development and the changes in these normal molecular processes in AD, DVD and other retrogenic dementias" and that activation of "mitogenic molecular markers including the mitogen-activated protein kinase (MAPK) cascade, cyclins, and cyclin dependent kinases" has been "related to the phosphorylation and hyperphosphorylation of tau, and, consequently,

the development of neurofibrillary changes in AD" has been carefully considered, but still fails to adequately define or delimit those diseases that are intended to be within the scope of the present claims. The Examiner alleges that the word "related" is a term that is open to subjective interpretation as to whether a particular disease state is considered to be a condition associated with retrogenesis and in light of such a subjective interpretation, and the fact that the presently claimed subject matter and corresponding disclosure does not particularly point out the degree or type of relationship that a given retrogenic condition may have to those that are presently claimed and still be considered a retrogenic disease as intended by the claims, the metes and bounds of the term and, thus, the claim, cannot be identified. The Examiner notes that should Applicant intend the treatment of specific conditions determined to be related to retrogenesis, Applicant should amend the claims to add such limitations.

Though the meaning of the term is specifically and clearly defined in paragraph [0023] of the specification, Applicant herein removes the offending "related" in order to clarify the claim language further. "Related retrogenic diseases" or "retrogenic diseases" refers to conditions which result from, or are related to, the hyperphosphorylation of tau and the resulting neurofibrillary tangles. For example, these include the tauopathies such as frontotemporal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy, Down's syndrome, dementia pugilistica, multisystem atophy, Niemann-Pick disease type C, and Tangle only dementia. It also includes disorders which follow the retrogenic clinical course as well as being associated with hyperphosphorylated tau. These include Parkinson's dementia, and normal pressure hydrocephalus. Sabbagh, *et al.*, *Parkinsonism and Related Disorders,* 2005, 11: 311 – 315; Golomb, *et al.*, *Journal of Neurology, Neurosurgery, and Psychiatry*, 68, 778-781; O'Brien, *et al.*, *Lancet Neurology,* 2003, 2:89-98; Reisberg, *et al.*, *International Psychogeriatrics*, 2003, 15, Suppl.1, 231-239.

In support of the clarity of the claim language "retrogenic diseases", Applicant submits that the U.S. Government Center for Medicare and Medicaid Services (CMS), has mandated the retrogenically based functional stages of AD procedure (FAST procedure as discussed in paragraph [0023]) for certain purposes. *See, e.g.* U.S. government, Health Care Financing Administration (HCFA) Medicare, Medicaid, "Hospice– Determining Terminal

Status in Non-Cancer Diagnoses – Dementia, Policy Number: (YPF # 163) (Y Med # 20)," *The Medicare News Brief (A Publication for all Medicare Part B Providers)*, Issue No. MNB – 98-7, September 1998. Further, these corresponding global stages of AAMI, MCI, and AD are used presently by the major worldwide organization in the field, the Alzheimer's Association, to explicate the nature of the evolution and course of these conditions. *See, e.g.* "Stages of Alzheimer's Disease": Five pages describing Dr. Reisberg's seven stages of the Global Deterioration Scale (GDS) in detail. (www.alz.org/AboutAD/Stages.asp) The term "mild cognitive impairment" (MCI), was first used and described in association with Global Deterioration Scale (GDS) (Reisberg *et al.*, 1982) stage 3. *See, e.g.* Reisberg *et al., American Journal of Psychiatry,* 1982, 139:1136-1139; Gauthier *et al., Lancet*, 2006, 367: 1262-1270. The clinical definition of Age Associated Memory Impairment (AAMI), has been associated from, the beginning, with Global Deterioration Stage 2, a stage of Subjective Cognitive Impairment (SCI). *See, e.g.* Reisberg *et al., Developmental Neuropsychology,* 1986, 2:401-412. The current international consensus that the AAMI, MCI, AD, CVD and other retrogenic processes are amenable to clinical diagnosis has been closely associated with Global Deterioration Scale (GDS) and FAST clinical descriptions. *See, e.g.,* Reisberg *et al., International Psychogeriatrics*, 1997, 9 (Suppl. 1): 11-38. These clinical descriptions of the Global Deterioration Scale and the Functional Assessment Staging (GDS/FAST) procedure have been used in pivotal trials which have formed the basis for approvals of two of the four AD treatments currently marketed in the U.S. and worldwide. *See, e.g.* Reisberg *et al., Alzheimer Disease and Associated Disorders*, 1997, 11:(Suppl. 3), 8-18; Reisberg *et al., New England Journal of Medicine*, 2003, 348:1333-1341.

Rejections under 35 U.S.C. 103(a)

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 are rejected under 35 U.S.C. 103(a) as unpatentable over Duncan (WO 02/020022) in view of Lipton (WO 92/17168), Lee (US Patent No.: 6,043,244) and Gervais, *et al.*, (US Patent Publication No.: 2005/0031651) for the reasons made of record in the previous Office Action dated July 14, 2005, and further in view of Morris, *et al.*, ("Mild Cognitive Impairment Represents Early-State Alzheimer's Disease", 2001), cited in response to Applicant's remarks.

The Examiner alleges that newly added claims 67 and 69-70 are properly included in the present rejection because the combination of minocycline (or a tetracycline compound), salicylates and memantine for the treatment of Alzheimer's disease or other cognitive disorders would have been obvious to one of ordinary skill in the art because each was separately known to have efficacy in the treatment of Alzheimer's disease and would have been reasonably expected to have, at minimum, additive, if not synergistic, effects when combined. Furthermore, the Examiner alleges that the reasonable expectation of additive, if not synergistic, effects when combined for treating Alzheimer's disease would have also increased the reasonable expectation of success in treating other disorders associated with cognitive decline, since the other presently claimed cognitive disorders were known to have similar pathophysiological manifestations as Alzheimer's disease (i.e., related to amyloid peptide) and would have been reasonably expected to react similarly to such a therapeutic combination of agents as Alzheimer's disease itself.

1. The requirements of a proper prima facie case of unpatentability

As the Examiner knows, in order to establish a proper *prima facie* case of obviousness, the Examiner must establish that there is a suggestion or motivation to modify the references or to combine the reference teachings; there must be a reasonable expectation of success; and the references or combination of references must teach or suggest all of the claim limitations (*see, e.g.,* MPEP § 2142). The teachings or suggestions to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cr. 1991)). The arguments advanced by the Examiner fail to meet all of these criteria.

2. Regarding Duncan

Duncan teaches a method of treating or preventing a disease in a mammal comprising administering an amount of a tetracycline compound sufficient to downregulate microglial expression in the mammal, the disease being Alzheimer's disease, Guillian-Barre Syndrome, adrenoleukodystrophy, Parkinson's disease, or amyotrophic lateral sclerosis. Duncan also teaches a method of downregulating microglial expression in a mammal by administering an

effective amount of a tetracycline compound. Further, Duncan teaches a method of inhibiting inflammatory activity associated with microglial activation and production by administering an effective amount of a tetracycline compound. Some of the fundamental differences between the instant invention and the teachings of Duncan may be summarized as follows:

1. Duncan does not teach treating with a cell cycle inhibitor;
2. Duncan does not teach treating with a cell cycle inhibitor in combination with an anti-inflammatory agent;
3. Duncan does not teach treating with a cell cycle inhibitor in combination with an anti-inflammatory agent and a inhibitor of glutamate induced excitotoxicity;
4. Duncan does not teach treating with a cell cycle inhibitor that is capable of inhibiting neuronal cell cycle progression into a synthesis (S) phase;
5. Duncan does not teach treating with a cell cycle inhibitor that inhibits cell cycle progression at or prior to entry of a neuronal cell into, an early growth (G_1) phase.

In omitting mention of treating with an inhibitor of glutamate induced toxicity, Duncan omits mention of memantine, neramexane, amantidine, riluzole, MK801, ketamine, dextromethorphan, dextrophan, phencyclidine, and dexanabinol. Duncan does not propose treating either age associated memory impairment (AAMI), mild cognitive impairment (MCI), cerebrovascular dementia or other retrogenic dementias. Duncan's approach for treating diseases in mammals with anti-inflammatory agents is vastly different from the present invention which features treating AAMI, MCI, AD, cerebrovascular dementia or other retrogenic dementias with cell-cycle inhibitors, in combination with anti-inflammatory agents, and in combination with inhibitors of glutamate induced excitotoxicity. The science behind these approaches is very different and the pathologic endpoints, (i.e., inhibition of cell cycle progression, reduction of tau hyperphosphorylation, vs inhibition of microglial expression) are very different.

3. Regarding Gervais

Gervais teaches therapeutic formulations for the treatment of beta-amyloid related disease. There is absolutely no factual or conceptual overlap between the teachings of Gervais and the present invention. The present invention is based in part upon the following discoveries:

1. The discovery and validation of the retrogenic process in AD;

2. The discovery that metabolic deficits occur in the brain with the evolution of MCI and AD;

3. The discovery of abnormalities in the cell cycle in aging and AD;

4. The discovery that metabolic deficits precede behavioral manifestations of AD;

5. The discovery that the retrogenic process and the cell cycle abnormalities can explain the pathologic nature of AD, including the cell losses in specific brain regions, and the neurofibrillary tangles; and

6. The discovery that the metabolic patterns in the brain of normal subjects and subsequent changes in AD, relate to the β-amyloid plaques in AD.

The latter discovery acknowledges the occurrence of the β-amyloid plaques in AD. However, there are no implications with respect to the pathogenic role of these findings in the patient with any of the disorders amenable to the treatment methods of the present invention. The present invention is not based upon any possible benefit or disadvantage of treating the β-amyloid plaque occurrence.

4. Regarding Lipton

Lipton teaches treatment of nervous system disorders, particularly disorders mediated by the NMDA subtype of excitatory amino acid receptor. Lipton makes use of the discovery of the utility of excitatory amino acid receptor antagonists. The present invention is much broader in scope than the teachings of Lipton. As such, the teachings of Lipton do not suggest the instant invention. Specifically, the present invention is directed to treating conditions with cell cycle inhibitors, in combination with inhibitors of brain inflammation and inhibitors of glutamate induced excitotoxicity. The present invention is not directed to treating glutamate induced excitotoxicity without this combination. Glutamate induced excitotoxicity is only one part of a much broader pathogenic mechanism to which the treatment methods of the present invention are directed.

5. Regarding Lee

Lee teaches that "the stimulation of β-adrenergic receptors, which activate cAMP formation, give rise to increased APP and GFAP synthesis in astrocytes." (*See* abstract, 1st sentence). Basically, the treatment of Lee entails a neurochemical approach and the reduction of APP (amyloid precursor protein). APP is presently believed to be a useful protein which frequently results in fragments, such as those resulting from alpha-secretase proteolytic processing, which promote neuronal growth and development. Hence, treatments that inhibit APP are probably very harmful to humans. The approach of Lee has no relationship whatsoever to the treatment methods according to the present invention.

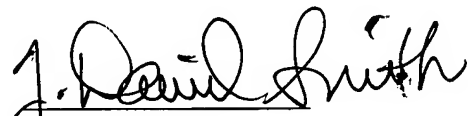
Fees

No additional fees are believed to be necessitated by the foregoing response. However, if this is in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 114, to effect a resolution.

Respectfully submitted,



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